REMARKS

Status of the Claims

Pending claims

Claims 1 to 82 are pending (claims 34 to 82 were added in Applicants' response of June 01, 2005).

Claims canceled and added in the instant amendment

Claims 83 to 93 are added and claims 31, 32, 65, and 72 to 82, are canceled, without prejudice or disclaimer. Thus, after entry of the instant amendment, claims 1 to 30, 33 to 64, 66 to 71 and 83 to 93 will be pending and under consideration.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for claims comprising use of the term "or a precursor thereof" can be found, inter alia, in the paragraph of lines 6 to 19, of page 8, of the specification:

> Of course any cell can be used in the practice of the invention. Preferably, the cell to be transduced is a eukaryotic cell. More preferably, the cell is a primary cell. Cell lines, however, may also be transduced with the methods of the invention and, in many cases, more easily transduced. In one preferred embodiment, the cell to be transduced is a primary lymphocyte (such as a T lymphocyte) or a macrophage (such as a monocytic macrophage), or is a precursor to either of these cells, such as a hematopoietic stem cell. Other preferred cells for transduction in general are cells of the hematopoietic system, or, more generally, cells formed by hematopoiesis as well as the stem cells from which they form and cells associated with blood cell function. Such cells include granulocytes and lymphocytes formed by hematopoiesis as well as the progenitor pluripotent, lymphoid, and myeloid stem cells. Cells associated with blood cell function include cells that aid in the functioning of immune system cells, such as antigen presenting cells like dendritic cells, endothelial cells, moncytes, and Langerhans cells. In a preferred embodiment, the cells are T lymphocytes (or T cells), such as those expressing CD4 and CD8 markers. (emphasis added)

Support for claims directed to the stable transduction of primary CD34+ hematopoietic stem cells can be found, inter alia, in lines 20 to 23, of page 8 ("... the cell is a primary CD4+ T lymphocyte or a primary CD34+ hematopoietic stem cell. ... (emphasis added)).

Support for claims directed to transduction of mixed or pure cell cultures, a tissue or an organ system, can be found, inter alia, in the specification from line 24, page 8, to line 31, page 9.

Support for claims directed to use of pseudotyping to broaden the host cell range of a viral vector of the invention, can be found, inter alia, in the specification on page 8, lines 21 to 22 ("... given that the viral vectors for use in the invention may be pseudotyped with Vesicular Stomatitis Virus envelope G protein (as discussed below), any cell can be transduced via the methods of the present invention"); and, page 16, line 30, to page 17, line 22:

The viral vectors used in the present invention may also result from "pseudotype" formation, where co-infection of a cell by different viruses produces progeny virions containing the genome of one virus encapsulated within an outer layer containing one or more envelope protein of another virus. This phenomenon has been used to package viral vectors of interest in a "pseudotyped" virion by co-transfecting or co-infecting a packaging cell with both the viral vector of interest and genetic material encoding at least one envelope protein of another virus or a cell surface molecule. See U.S. Patent 5,512,421. Such mixed viruses can be neutralized by anti-sera against the one or more heterologous envelope proteins used. One virus commonly used in pseudotype formation is the vesicular stomatitis virus (VSV), which is a rhabdovirus. The use of pseudotyping broadens the host cell range of the virus by including elements of the viral entry mechanism of the heterologous virus used. ... (emphasis added)

Accordingly, no new matter has been added and the amendment can be properly entered.

The Group Restriction Requirement

The Patent Office alleged that the pending claims of the application are directed to six separate and distinct inventions (groups a through f) under 35 U.S.C. §121, as set forth on page 1 of the instant office action:

Group I (claims 1-30, 33-64, and 66-71) drawn to in vitro/ex vivo methods of transducing primary cells of the hematopoietic system using a lentiviral vector and cell surface binding molecule, classified in class 435, subclass 456;

Group II (claims 31 and 32) drawn to a method for the introduction of transduced cells into a living subject, classified in class 435, subclass 325;

Group III (claim 65) drawn to a method of introducing a transduced cell into a tissue, organ, blastocyst, or embryonic stem cell, classified in class 435, subclass 325;

Group IV (claims 72 and 73) drawn to a method for the stable transduction of hematopoietic stem cells isolated from an HIV-infected individual, classified in class 435, subclass 456;

Group V (claims 74-77 and 80-82) drawn to a composition formulated for the treatment of a viral infection comprising a transduced cell, classified in class 435, subclass 325; and

Group VI (claims 74, 75, 78-80, and 82) drawn to a composition formulated for the treatment of a tumor comprising a transduced cell, classified in class 435, subclass 325.

The Group Election

Applicants hereby elect Group I, claims 1 to 30, 33 to 64, and 66 to 71, including new claims 83 to 92.

Applicants expressly reserve their right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application, or an application claiming priority from this application.

The Species

The Patent Office has further alleged that the claims in Groups I, II or III are directed to patentably distinct species, as set forth on page 3 of the instant office action:

(1) The Office alleges that Applicants are required to elect and identify the precise structural/ functional characteristics of the lentiviral vector employed, including:

- specify origin, e.g., HIV-1, HIV-2, SIV, EIAV, etc.

- genomic structure, e.g., nef-deficient, tat-deficient, rev-deficient, pseudotyped with VSV G envelope, etc.;

(2) The Office alleges that Applicants are required to elect and identify a specific cell surface binding molecule, e.g., an FLT-3, a TPO, a Kit ligand, etc.;

(3) The Office alleges that Applicants are required to elect a single cell target, e.g., $CD4^+$, $CD8^+$, $CD34^+$, etc.

The Species Election

In response, Applicants elect the following species, all with traverse:

(1) Regarding election and identification of the precise structural/ functional characteristics of the lentiviral vector employed: for "origin" Applicants elect a vector derived from HIV-1, with traverse; and for "genomic structure" Applicants elect a vector derived from wild type HIV-1, with traverse.

(2) Regarding election and identification of a specific cell surface binding molecule, Applicants elect αCD3, with traverse; and optionally elect the combination of immobilized αCD3 and αCD28, noting the embodiment of the invention described in Examples II, III, IV and V, pages 32 to 35, of the specification used beads comprising immobilized αCD3 and αCD28.

(3) Regarding election of a single cell target cell, Applicants elect $CD4^+$ cells, with traverse.

When the elected species is held to be allowable, Applicants are entitled to consideration (examination) of additional species; if all species are held to be allowable, a generic claim should be allowed (MPEP §809.02(c); pg 800-50, 8th Edition, August 2001).

Reasons to reconsider and withdraw restriction requirement

Applicants respectfully request the Patent Office reconsider and, in part, withdraw the restriction requirement for the following reasons:

The Patent Office describes the invention of elected Group I, Group II and Group III as being drawn to methods that are patentably distinct because they use different lentiviral vectors or pseudovectors, and to methods that are patentably distinct because they stably transduce distinct cell types, and to methods that are patentably distinct because they use different cell surface binding molecules.

However, claim 1, after entry of the instant amendment, is directed to methods for stable transduction of primary cells of the hematopoietic system and/or hematopoietic stem cells

comprising contacting the surface of said primary cell or hematopoietic stem cells at the same time *in vitro* or *ex vivo* with both a lentiviral vector and at least one molecule which binds said cell surface, wherein at least about 75% of the cells are stably transduced after about seven to ten days, or at about 14 days.

Claim 34, after entry of the instant amendment, is directed to methods for stable transduction of primary cells of the hematopoietic system and/or hematopoietic stem cells comprising (a) isolating from an individual a primary cell of the hematopoietic system and/or a hematopoietic stem cell; and (b) contacting the primary cell or hematopoietic stem cell simultaneously *in vitro* or *ex vivo* with a lentiviral vector and an at least one molecule that physically interacts with a receptor, marker, or other recognizable moiety on the surface of the primary cell or hematopoietic stem cell, wherein greater than about 75% of the primary cells or hematopoietic stem cells are stably transduced after about seven to ten days, or at about 14 days, and optionally the cell surface binding molecule comprises a polypeptide, a lipid, a nucleic acid, a carbohydrate or an ion.

New claim 88 is directed to methods for stable transduction of a cell with a lentiviral vector comprising contacting the cell at the same time *in vitro* or *ex vivo* with a lentiviral vector and at least one cell surface binding molecule, wherein the lentiviral vector is pseudotyped, wherein the pseudotyping comprises co-transfecting or co-infecting a packaging cell with both the lentiviral vector genetic material and genetic material encoding at least one envelope protein of another virus or a cell surface molecule, wherein at least about 75% of the cells are stably transduced after about seven to ten days, or at about 14 days, and optionally at least 75% of the cells remain stably transduced after about 14 days.

Applicants respectfully submit that the invention of the elected Group I comprises methods for stable transduction of cells, including hematopoietic system and/or hematopoietic stem cells, comprising simultaneous contact of any member of a genus of lentiviral vectors and any member of a genus of cell surface binding molecules or molecules that physically interact with a receptor, marker, or other recognizable moiety on the surface of the primary cell or hematopoietic

stem cell. Thus, the Patent Office has erroneously incorporated into the independent claims 1, 34 and 88, the limitations of dependent claims, thereby improperly limiting what Applicants consider their invention.

For example, if the elected invention is limited to methods using vectors derived from HIV-1, e.g., wild type HIV-1, then the limitations of, inter alia, dependent claim 10 (wherein the lentiviral vector is derived from HIV-1 or HIV-2) or claim 13 (wherein the lentiviral vector is a chimeric vector comprising HIV sequences, wherein optionally the HIV sequences comprise HIV-1 and HIV-2 sequences), are improperly incorporated into the independent claims. Likewise, if the elected invention is limited to methods using vectors derived from HIV-1, the genus of vectors used in the elected methods would be improperly limited, e.g., the embodiments of claim 11 (wherein said lentiviral vector is a pseudotyped vector) or claim 12 (wherein said pseudotyped vector comprises the vesicular stomatitis virus G envelope protein) would be improperly excluded from the genus.

Similarly, if the elected invention is limited to methods using a specific cell surface binding molecule, such as the elected αCD3, or the optionally elected combination of immobilized αCD3 and αCD28, then the limitations of, inter alia, claim 18 (... a CD28 ligand) is improperly incorporated into the independent claims. Similarly, the alternative embodiment of, inter alia, dependent claim 7 (wherein said cell surface binding molecule is an antibody, an antigen binding fragment, a ligand or a cell surface molecule), dependent claim 18 (wherein said at least one cell surface binding molecule comprises a molecule selected from the group consisting of an FLT-3 ligand; a TPO ligand Kit ligand; antibodies ...), or claim 19 (wherein said at least one cell surface binding molecule comprises a molecule selected from the group consisting of FLT-3 ligand, TPO ligand and Kit ligand ...) would be erroneously excluded, thereby improperly limiting what Applicants consider their invention.

If the elected invention is limited to methods using a single cell target cell, e.g., the elected $CD4^+$ cells, then the limitations of, inter alia, dependent claim (wherein said primary hematopoietic cell is a CD4 positive cell or is a hematopoietic stem cell of a CD4 positive cell) is

improperly incorporated into the independent claims. Likewise, if the elected invention is limited to methods using a single cell target cell, the genus of cells transduced by the elected methods would be improperly limited, e.g., the embodiments of claim 15 (wherein said primary cell of the hematopoietic system or hematopoietic stem cell is a lymphocyte or a precursor thereof) or claim 17 (wherein the primary cell of the hematopoietic system or hematopoietic stem cell is a CD34 positive cell or a precursor thereof) would be improperly excluded from the genus.

The procedure for handling applications that include generic claims is set forth in 37 CFR §1.146. This rule provides that "[i]n the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable." (emphasis added)

As stated in MPEP § 809.02(a), "[u]pon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141." Thus, where generic claims are present, an applicant can be required to elect a species for initial examination, but the generic claims are still subject to examination to determine whether such generic claims are allowable (MPEP §809.02(a), 8th ed., rev. 2, May 2004, pg 800-49).

In the instant restriction requirement, this required procedure is not being followed. Claims 1, 34 and 88 are proper generic claims within the requirements set forth in 37 CFR § 1.141. Claim 1 satisfies the definition of a generic claim as set forth in MPEP §806.04(d), in that it includes limitations that are not present in all claims that depend from it. Therefore, an election of species requirement is permissible, but a restriction requirement is not. (MPEP §806.04(d), 8th ed., rev. 2, pg 800-41).

Moreover, because this "patentably distinct" species/restriction requirement splits claim 1 into multiple groups, the restriction requirement is improper as a matter of law. The courts have long held that the section of the patent statute that authorizes restriction practice, *i.e.*, 35 U.S.C. 121,

provides no legal authority for not examining a broad generic claim. See, In re Weber, 198 USPQ 328, 331 (CCPA 1978); In re Haas, 179 USPQ 623, 624-625 (*In re Haas I*) (CCPA 1973) and In re Haas 198 USPQ 334-337 (In re Haas II) (CCPA 1978). As stated in In re Weber:

> "The discretionary power to limit one applicant to one invention is no excuse at all for refusing to examine a broad generic claim—no matter how broad, which means no matter how many independently patentable inventions may fall within it." 198 USPQ 328 at 334. (emphasis added)

In a case such as the instant case, where a claim is generic, a restriction requirement is tantamount to a rejection of the claim. The CCPA made this point very clear in In re Haas I:

> "We find that the action taken by the examiner did in fact amount to a rejection. . . . Those claims were withdrawn from consideration not only in this application but prospectively in any subsequent application because of their content. In effect there had been a denial of patentability of the claims. Presumably only by dividing the subject matter into separate, and thus different, claims in plural applications could an examination of the patentability of their subject matter be obtained." 179 USPQ at 625.

If the instant restriction requirement is allowed to stand, Applicants will not be accorded "the basic right of the applicant to claim his invention as he chooses." In re Weber, 198 USPQ at 331. In In re Weber, the CCPA stated that "[a]s a general proposition, an applicant has a right to have *each* claim examined on the merits" (198 USPQ at 331, emphasis in original). The Court went on to state that:

> "If . . . a single claim is required to be divided up and presented in different applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification." 198 USPQ at 331.

Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas,* 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. MPEP §803.02, 8th ed., rev. 2, May 2004, pg 800-4. Even if Applicants were to file

multiple divisional applications in addition to the instant application to obtain coverage for each of the alleged patentably distinct species, we would not have the opportunity to have our broader generic claim examined, i.e., we would not have the opportunity to have that which Applicants regard as their invention examined. The claims of the various divisional applications would be limited to the particular species set forth in the respective groups. One seeking to avoid infringement could simply choose a vector that is not specifically disclosed in the application. In effect, the restriction requirement is reading into Applicants' independent claims limitations that are not present in the claims as filed. The full scope of claim 1 as filed and pending, for example, would never be considered under the current species restriction requirement. Only the dependent claims which are set forth in the respective groups would be examined.

Applicants therefore respectfully request that the instant restriction requirement with respect to "patentably distinct species" be withdrawn and treated as though it were a species election under the procedure set forth in MPEP 809.02(a). Applicants request that, upon allowance of a generic claim, the remainder of the species be included as permitted by 37 C.F.R. § 1.141(a).

Pursuant to 37 C.F.R. § 1.144, Applicants reserve the right to petition for review of the restriction requirement at any time prior to appeal. Applicants also submit that because the instant restriction requirement is tantamount to a rejection of the generic independent claims (claim 1, claim 34, and new claim 88) the restriction requirement is appealable to the Board of Patent Appeals and Interferences. In re Haas I. If the instant restriction requirement is allowed to stand, Applicants will not be accorded "the basic right of the applicant to claim his invention as he chooses." In re Weber. It is improper for the Office to refuse to examine that which Applicants regard as their invention. MPEP §803.02, 8th ed., rev. 2, May 2004, pg 800-4.

Accordingly, Applicants respectfully request reconsideration of the restriction requirement and request that the restriction requirement with respect to the "patentably distinct species," as discussed above, be withdrawn and treated as though it were a species election under the procedure set forth in MPEP 809.02(a).

CONCLUSION

Applicants have respectfully requested reconsideration of the restriction requirement; in particular, they have requested that the restriction requirement with respect to the "patentably distinct species," as discussed above, be withdrawn and treated as though it were a species election under the procedure set forth in MPEP 809.02(a).

It is believed that the all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

In the unlikely event that the transmittal form is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing 397272000401. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Dated: September 16, 2005

Respectfully submitted,

By _____
Gregory P. Einhorn
Registration No.: 38,440
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
(858) 720-5133 (direct line)
Email: geinhorn@mofo.com

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